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Direct Functionalization of Tetrahydrofuran and 1,4-Dioxane: Nickel-Catalyzed Oxidative C(sp^3)–H Arylation**

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Tetrahydrofuran (THF) and 1,4-dioxane are important basic chemical feedstocks. Moreover, such five- or six-membered ring moieties frequently occur within the framework of many important organic compounds (selected examples are shown in Figure 1).[1] However, to construct tetrahydrofuran or 1,4-dioxane rings in complex organic molecules is sometimes challenging and usually requires cumbersome synthetic routes. Therefore, direct functionalization of THF or 1,4-dioxane to introduce these simple molecules into complex organic compounds is important for the synthetic chemistry community. Owing to their lack of reactivity under many reaction conditions, direct functionalization is a challenging task, which is why these species are among the most widely used solvents in both academia and industry. Consequently, reports employing such simple ether derivatives in C–C bond forming reactions to construct higher-functionalized ethers are rare.[2] Therefore, it is vital to investigate the direct utilization of such simple ether derivatives, which bear C(sp^3)–H bonds, in C–C bond forming reactions.

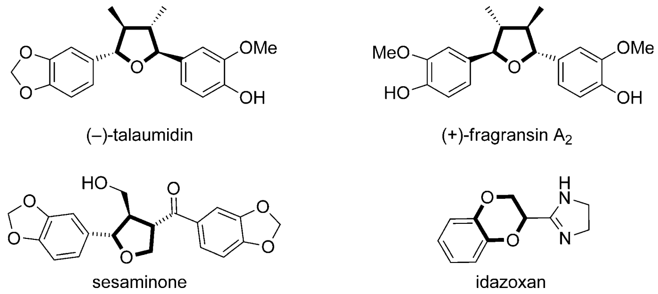

Figure 1. Representative organic compounds containing tetrahydrofuran and 1,4-dioxane moieties.

C–C bond forming reactions involving transition-metal-catalyzed C–H functionalization have attracted much attention owing to their remarkable potential for atom-economy and environmental sustainability.[3] Thus far, sustainable progress has been made in the area of oxidative C(sp)–H and C(sp^2)–H couplings for various C–C bond forming reactions.[4] However, oxidative couplings involving C(sp^3)–H bonds remain challenging.[5] In the past few years, several Pd- and Ru-catalyzed oxidative arylation reactions of C(sp^3)–H bonds have been revealed, which involve directing groups such as pyridines, carboxylic acids, and amidines.[6] Moreover, the oxidative arylation of C(sp^3)–H bonds adjacent to nitrogen atoms has also been demonstrated in recent years.[7] However, to the best of our knowledge, only isolated examples of the oxidative arylation of C(sp^3)–H bonds adjacent to oxygen atoms (ether derivatives) with aryl nucleophiles have been reported to date.[2b,c]

For ether derivatives, the C(sp^3)–H bonds adjacent to oxygen atoms have a relatively lower bond dissociation energy (BDE), which indicates that homolytic cleavage of these C–H bonds will easily take place. Therefore, it is possible to activate this type of compound by a single electron transfer process. First-period transition-metal catalysts, such as Cu and Fe salts, combined with peroxides were the preferred choice for promoting heteroatom-adjacent Csp^3–H bond cleavage by a single electron transfer process, for example, CDC couplings.[8] As another widely applied first-row transition-metal catalyst, nickel has been used in organic synthesis to construct various functionalized molecules and materials owing to its low cost and easy availability.[9] However, there have been few reports of oxidative-couplings utilizing a nickel catalyst.[10] Moreover, no reports of nickel-catalyzed oxidative C(sp^3)–H functionalization are known. Herein, we demonstrate a novel nickel-catalyzed oxidative arylation of the *ortho*-Csp^3–H bond adjacent to the oxygen atom of THF or 1,4-dioxane.

Our initial efforts focused on the direct coupling of phenylboronic acid (**1a**) with tetrahydrofuran (**2a**) using [Ni(acac)$_2$] as the catalyst precursor. In the presence of [Ni(acac)$_2$] (10 mol %), PPh_3 (20 mol %), K_3PO_4 (2 equiv) and di-*tert*-butyl peroxide (DTBP; *t*BuOO*t*Bu; 2 equiv) in THF (1.0 mL) at 80 °C with stirring for 16 h, we obtained the desired product in 35 % yield (Table 1, entry 1). A higher temperature improved the yield to 57 % (Table 1, entry 2). Further optimization showed that a dilute solution improves the reaction yield, which ultimately increased to 69 % (Table 1, entry 3). With the participation of K_3PO_4 (1.0

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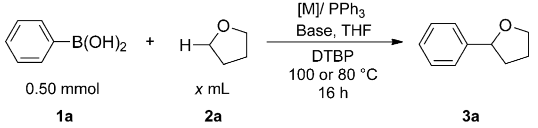
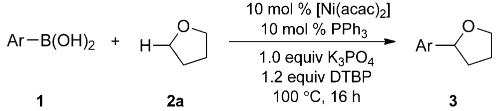
Table 1: Optimization of reaction conditions for the nickel-catalyzed oxidative arylation of THF with **1a**.[a]

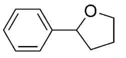
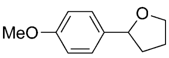
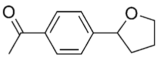
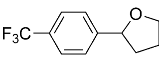
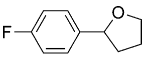
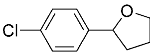
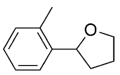
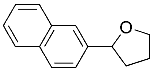


Entry	[M]/PPh$_3$	Base	x [mL]	Yield [%][b]
1[c,d]	[Ni(acac)$_2$]/2PPh$_3$	K_3PO_4	1.0	35
2[d]	[Ni(acac)$_2$]/2PPh$_3$	K_3PO_4	1.0	57
3[d]	[Ni(acac)$_2$]/2PPh$_3$	K_3PO_4	2.0	69
4	[Ni(acac)$_2$]/PPh$_3$	K_3PO_4	2.0	71
5	[Ni(acac)$_2$]/PPh$_3$	NaOAc	2.0	trace
6	[Ni(acac)$_2$]/PPh$_3$	KO*t*Bu	2.0	n.d.
7	[Ni(acac)$_2$]/PPh$_3$	K_2CO_3	2.0	trace
8	[Ni(acac)$_2$]/PPh$_3$	$K_3PO_4 \cdot 3\,H_2O$	2.0	34
9	[Ni(acac)$_2$]/PPh$_3$	–	2.0	n.d.
10	[Ni(acac)$_2$]/PPh$_3$	K_3PO_4	3.0	75
11[e]	**[Ni(acac)$_2$]/PPh$_3$**	**K_3PO_4**	**3.0**	**88**
12[e]	[Co(acac)$_3$]/PPh$_3$	K_3PO_4	3.0	trace
13[e]	[Cu(acac)$_2$]/PPh$_3$	K_3PO_4	3.0	< 5
14[e]	[Fe(acac)$_3$]/PPh$_3$	K_3PO_4	3.0	< 5
15[e]	[Ni(acac)$_2$]/–	K_3PO_4	3.0	59
16[e]	–/PPh$_3$	K_3PO_4	3.0	n.d.

[a] Unless otherwise noted, the reaction was carried out with **1a** (0.50 mmol), **2a** (2.0 mL), [Ni(acac)$_2$] (0.05 mmol), PPh$_3$ (0.05 mmol), base (0.50 mmol), and DTBP (0.60 mmol) at 100°C for 16 h. [b] Yield of isolated product. [c] 80°C. [d] 1.0 mmol base, 1.0 mmol DTBP was used. [e] PhB(OH)$_2$ was treated as in Ref. [11]. n.d. = not detected. DTBP = di-*tert*-butyl peroxide.

Table 2: Substrate scope for the nickel-catalyzed oxidative arylation of THF with arylboronic acids.[a]



Entry	Product	3	Yield [%][b]
1		**3a**	88
2		**3b**	93
3		**3c**	78
4		**3d**	52
5		**3e**	86
6		**3f**	84
7		**3g**	84
8		**3h**	52

[a] Reaction conditions : **1** (0.50 mmol), **2a** (3.0 mL), [Ni(acac)$_2$] (10 mol%), PPh$_3$ (10 mol%), K_3PO_4 (0.50 mmol), and DTBP (0.60 mmol) at 100°C for 16 h. [b] Yield of isolated product.

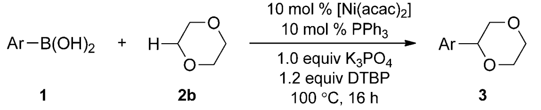
equiv) and DTBP (1.2 equiv), we unexpectedly isolated the target product in 71 % yield (Table 1, entry 4). Further base screening revealed that K_3PO_4 was the best choice for this reaction. NaOAc, KO*t*Bu, and K_2CO_3 afforded almost no product (Table 1, entries 5–7). A stoichiometric amount of water played a negative role in this reaction, as $K_3PO_4 \cdot 3\,H_2O$ afforded only 34 % yield of the target product (Table 1, entry 8). Understandably, reaction did not proceed in the absence of base (Table 1, entry 9). Further diluting the reaction system resulted in a slightly higher yield of 75 % (Table 1, entry 10). It is well known that arylboronic acids readily generate 2,4,6-triarylboroxin through dehydrative trimerization when exposed to air for an extended period of time. However, this compound showed no reactivity in this catalytic system. Excitingly, when we hydrolyzed it back to the arylboronic acid form[11] and added it to the standard reaction system, we isolated the desired product in a yield of 88 % (Table 1, entry 11). The nickel catalyst gave unparalleled performance in this reaction, other metal salts such as [Co(acac)$_3$], [Cu(acac)$_2$], and [Fe(acac)$_3$] were all ineffective (Table 1, entries 12–14). The absence of PPh$_3$ decreased the yield to 59 % (Table 1, entry 15). Furthermore, the reaction did not proceed without the nickel catalyst (Table 1, entry 16).

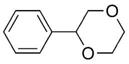
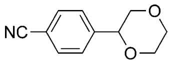
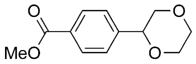
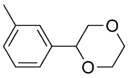
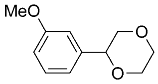
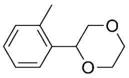
Usually, the homo-coupling of arylboronic acids is the main side reaction and the biaryls are inevitable byproducts under oxidative conditions. However, under the optimized conditions of this oxidative C(sp^3)−H arylation with arylboronic acids as the nucleophiles, only a trace amount of the homo-coupling product was detected and the cross-coupling product was selectively obtained.

With the optimized conditions in hand, we next explored the substrate scope of this nickel-catalyzed oxidative arylation reaction. Firstly, various arylboronic acids were coupled with tetrahydrofuran under the standard conditions (Table 2). Various functional groups were well tolerated. The desired coupling products were obtained in good to excellent yields. Arylboronic acids with an electron-rich *p*-OMe substituent (Table 2, entry 2) or with electron-deficient substituents such as *p*-Ac and *p*-CF$_3$ (Table 2, entries 3 and 4) all gave the desired products in satisfactory yields. Halogen substituents such as fluorine and chlorine were well tolerated, affording the corresponding arylation products in 86 % and 84 % yield, respectively (Table 2, entries 5 and 6). The reaction of *o*-tolylboronic acid with tetrahydrofuran proceeded well to give the target product in 84 % yield (Table 2, entry 7), thus demonstrating that sterics have little influence. Naphthalen-2-ylboronic acid is also a suitable substrate for this reaction (Table 2, entry 8).

As 1,4-dioxane is also a widely used solvent and an important ether derivative, we further applied this oxidative arylation conditions to this substrate. To our delight, good results were obtained with a variety of arylboronic acids (Table 3). Under the optimized conditions, phenylboronic acid coupled well with 1,4-dioxane to afford the desired product in 63 % yield (Table 3, entry 1). For arylboronic acids bearing strong electron-withdrawing groups such as *p*-CN and *p*-COOMe, the reactions proceeded smoothly to give the arylation products in 70 % and 57 % yield, respectively (Table 3, entries 2 and 3). Substituents in the *meta*-position, such as *m*-Me and *m*-OMe, were also well tolerated in this reaction (Table 3, entries 4 and 5). For sterically hindered

Table 3: Substrate scope for the nickel-catalyzed oxidative arylation of 1,4-dioxane with arylboronic acids.[a]



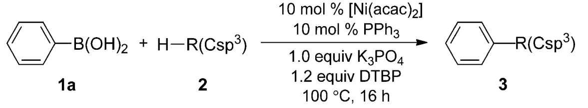
Entry	Product	3	Yield [%][b]
1		**3i**	63
2		**3j**	70
3		**3k**	57
4		**3l**	64
5		**3m**	50
6		**3n**	55

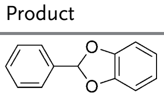
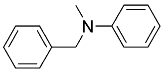
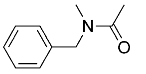
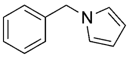
[a] Reaction conditions: **1** (0.50 mmol), **2b** (3.0 mL), [Ni(acac)$_2$] (10 mol%), PPh$_3$ (10 mol%), K$_3$PO$_4$ (0.50 mmol), and DTBP (0.60 mmol) at 100°C for 16 h. [b] Yield of isolated product.

substrates such as *o*-tolylboronic acid, reaction with 1,4-dioxane also proceeded well, albeit with a slightly lower yield (Table 3, entry 6).

As good results have been obtained for the coupling of arylboronic acids with simple ether derivatives such as tetrahydrofuran and 1,4-dioxane, we turned our attention to more functionalized ether substrates and other C(sp^3)−H sources. Delightfully, when we employed benzo[*d*][1,3]dioxole as a substrate, the coupling with phenylboronic acid afforded the desired product in 53% yield (Table 4, entry 1). Furthermore, it was found that not only the C(sp^3)−H bond adjacent to oxygen could be oxidatively arylated, but C(sp^3)−H bonds adjacent to nitrogen could also be successfully arylated. The substrate *N,N*-dimethylaniline, the oxidative arylation of which has not been thus far achieved in CDC reactions, coupled well with phenylboronic acid under our optimized conditions to give the arylated product in 71% yield (Table 4, entry 2). Moreover, for the frequently used aprotic polar solvent *N,N*-dimethylacetamide, the *N*-methyl group could also be selectively arylated to produce a good yield of the mono-arylation product (Table 4, entry 3). Furthermore, *N*-methyl pyrrole could also be activated to give the corresponding *N*-benzyl pyrrole, albeit in moderate yield (Table 4, entry 4).

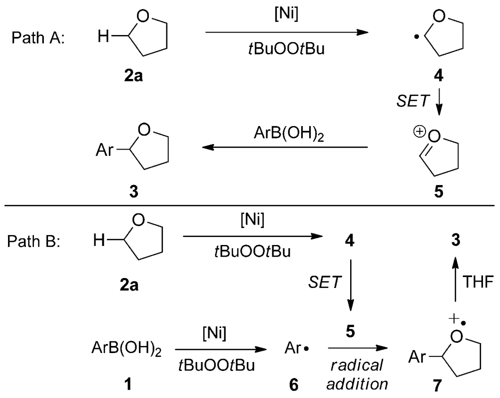
Table 4: Substrate scope for the nickel-catalyzed oxidative arylation of other C(sp^3)−H bonds with phenylboronic acid.[a]



Entry	Product	3	Yield [%][b]
1		**3o**	53
2		**3p**	71
3		**3q**	56
4		**3r**	45

[a] Reaction conditions: **1a** (0.5 mmol), **2** (2.0 mL), [Ni(acac)$_2$] (10 mol%), PPh$_3$ (10 mol%), K$_3$PO$_4$ (0.5 mmol), and DTBP (0.6 mmol) at 100°C for 16 h. [b] Yield of isolated product.

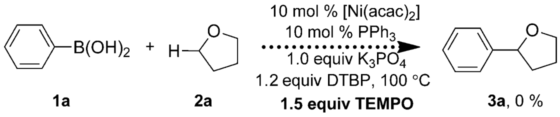
To our knowledge, the carbon-centered radical adjacent to the oxygen of tetrahydrofuran can be generated by H-abstraction with a *tert*-butoxyl radical formed by the transition-metal-initiated decomposition of peroxide.[12] This radical could be further oxidized to a cation,[13] whereas DTBP could react with transition-metal salts and further undergoes homolytic cleavage to afford a *tert*-butoxyl radical and high-valent metal hydroxide. In that case, the *tert*-butoxyl radical can promote the generation of an aryl radical from arylboronic acid.[14] Therefore, we propose two possible pathways (Scheme 1): A carbon-centered radical species adjacent to oxygen (**4**) can be initiated from THF in the presence of a nickel catalyst and DTBP, which could be further oxidized to form cation **5** through an initial SET (single-electron-transfer) step. Subsequently, the coupling of **5** with the pronucleophile arylboronic acid results in the desired product **3** (Scheme 1, Path A). Alternatively, in Path B, aryl radical **6** is generated with the aid of a nickel catalyst and DTBP. Subsequent radical addition to **5** generates oxygen-centered radical cation **7**. Finally, radical abstraction from tetrahydrofuran affords the desired product (Scheme 1, Path B).



Scheme 1. Proposed reaction mechanism.

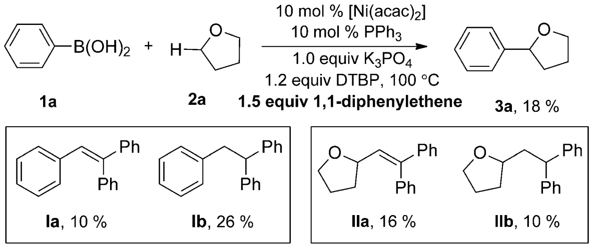
To confirm the radical pathway of this transformation, radical-trapping experiments were conducted. When using TEMPO as the radical-trapping reagent, formation of desired product **3a** was totally suppressed [Eq. (1)], thus revealing that this reaction probably proceeds by a radical pathway.

When another commonly used radical-trapping reagent, 1,1-diphenylethene, was employed, desired product **3a** was



(1)

obtained in only 18 % yield. We concurrently obtained both the coupling products of 1,1-diphenylethene with phenylboronic acids **Ia** and **Ib** in 10 % and 26 % yield, respectively, and the coupling products of 1,1-diphenylethene with tetrahydrofuran **IIa** and **IIb** in 16 % and 10 % yield, respectively [Eq. (2)]. The generation of products **Ia** and **Ib** indicates that aryl radical **6** is probably involved in this transformation, whereas **IIa** and **IIb** reveal that radical **4** is a probable intermediate in this process.[15] Therefore, path B (Scheme 1) is the more favored and feasible reaction pathway.



(2)

In conclusion, we have demonstrated the first nickel-catalyzed oxidative arylation of C(sp^3)–H bonds. Several substituted arylboronic acids and various C(sp^3)–H bonds were found to be suitable substrates for this novel transformation. Notably, this work provides an effective method for the introduction of simple ether derivatives to construct α-arylated ethers. Preliminary mechanistic studies suggest that this reaction is likely to proceed through a radical pathway. Further studies on the reaction mechanism are currently underway and will be reported in due course.

Experimental Section

General procedure: [Ni(acac)$_2$] (10 mol %), PPh$_3$ (10 mol %), anhydrous K$_3$PO$_4$ (0.50 mmol) and PhB(OH)$_2$ (0.50 mmol) were combined and sealed in an oven-dried tube equipped with a stir bar; the tube was then charged with nitrogen and THF (3.0 mL) was injected into the tube by syringe. After stirring for 5 min, DTBP (0.60 mmol) was injected into the reaction tube. The reaction was then heated to 100 °C and stirred for 16 h. Upon completion, the reaction was cooled down to room temperature and quenched with dilute HCl solution (2.0 M). After extraction with ethyl ether (3 × 5 mL), the organic layers were combined and dried over anhydrous Na$_2$SO$_4$. Pure product was obtained by flash column chromatography on silica gel (petroleum ether/ethyl acetate = 100:1). The yield of isolated product was 88 %.

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Keywords: C-H functionalization · nickel · oxidative coupling · radical reactions · tetrahydrofuran

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[11] First, the arylboronic acid was dissolved in aqueous NaOH solution (2 M), then excess aqueous HCl solution (2 M) was added to the system, producing a large amount of white precipitate. The pure product was obtained by suction filtration and drying under vacuum.

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C-H Functionalization

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Direct Functionalization of Tetrahydrofuran and 1,4-Dioxane: Nickel-Catalyzed Oxidative $C(sp^3)-H$ Arylation

CHoose nickel: The nickel-catalyzed oxidative arylation of $C(sp^3)-H$ bonds has been achieved. Several substituted arylboronic acids and various $C(sp^3)-H$ bonds were found to be suitable substrates for this novel transformation, which is likely to proceed through a radical pathway. This method allows the introduction of simple ether derivatives to construct α-arylated ethers. FG = functional group.